Obesity has become a worldwide public health problem affecting millions of people. This is a chronic, stigmatized, and costly disease, rarely curable and is increasing in prevalence to a point today where we define obesity as an epidemic disease that not only in developed but also on developing countries. The pathogenesis of obesity is largely unknown, especially about energy regulatory mechanism that involved wide area of neuroendocrinology that is very interesting but very complex and makes internists “refuse” to learn. Obesity occurs through a longstanding imbalance between energy intake and energy expenditure, influenced by a complex biologic system that regulates appetite and adiposity. Obesity influences the pathogenesis of hypertension, type 2 diabetes, dyslipidemia, kidney, heart, and cerebrovascular disease. It is very wise for every internist to learn the pathogenesis and treatment of this worldwide diseases. Until now, the available treatments, including drugs, are palliative and are effective only while the treatment is being actively used; and besides so many side effects reported.

**Key words**: obesity, pathogenesis, appetite, energy, adiposity, pharmacologic treatment.

**INTRODUCTION**

Obesity is a condition of excess adipose tissue in the body. The main diagnosis criteria for obesity among Asians is body mass index (BMI) ≥ 25 kg/m². Primary obesity is referred to as a condition where calorie intake exceeds basal metabolic rate, while secondary obesity occurs as a result of disorders such as hypogonadism and hypothyroidism. The prevalence of obesity in UK in 1998 was 17% (male) and 21% (female). In US (2001), obesity affected 20%-30% of population. In Indonesian population in Jakarta (1992-1993), obesity was found 10.9% (men) and 24% (women). In Bali, a survey conducted in Jenah-Peguyengan Kangin, Denpasar (urban area) in 1999 revealed prevalence of obesity 1.5%, while a study in Sangit, Buleleng district, found total prevalence of 25.3%.

The role of obesity, especially central obesity in type 2 diabetes mellitus (DM) and cardiovascular disease, has long been recognized. Meanwhile, several studies on the role of obesity in malignancy are still ongoing.

Recent studies showed that aside from fat tissue function as excess energy storage, but also as endocrine organ which produces various substances that affect body metabolism.

Etiology of obesity is often difficult to be determined. It is important to understand the pathogenesis of obesity specially energy regulation mechanism in order to provide appropriate management of obesity.

**PATHOGENESIS OF OBESITY**

The definite etiologic cause of obesity remains unclear. There are 3 main factors involved in the pathogenesis of obesity which are related to one another in a complex interaction.

**GENETIC FACTOR**

It is estimated about 30% and 50% of body weight gain is due to genetic factor. Study on families of obese patients had proven the existence of significant relationship of BMI between members of family among one generation. Until recently, we have identified 7 genetic disorders which cause obesity in human. They are gene signals of leptin, leptin receptor, melanocortin receptor 4 (MC4), alpha-melanocyte stimulating hormone (α-MSH), prohormone convertase 1 (PC-1), proopiomelanocortin receptor (POMC), peroxisome proliferators activated receptor gamma (PPAR-γ) gen. These genetic disorders consist of:

1. Monogenic disorder
In obesity due to single gene disorder, BMI may reach as high as > 60 kg/m², and has occurred since childhood. For example Prader-Willi syndrome which is caused by disappearance of material expression of paternal active genome in chromosome 15q11-13. The manifestation of the syndrome is short gesture, fat deposition in upper body, mental retardation, and hypogonadism. This disorder is very rarely found.  

2. Multigenic disorder

Obesity phenotype is presumed as the result of simultaneous interaction of genetic disorders and environment factor. Various genes that have been mentioned above are responsible for fat distribution, energy expenditure during activity and rest, eating habit, lipase protein activity, basal metabolic rate, insulin induced-fat synthesis and decreased effect of thermogenic factor of the food.

ENVIRONMENT FACTOR

Environment factors that contribute to obesity are factors that cause increased food intake and decreased physical activity. Those factors are listed in table 1.

Table 1. Environment Factors Contributing to Obesity

| Environment factors suggested to promote overeating |
|---------------------------------
| Portion size                  |
| High fat/energy dense foods   |
| High glycemic index of foods  |
| Soft drinks                   |
| Sugar                        |
| Fast foods                    |
| Snack foods                   |
| Low calcium                  |
| Accessibility of food         |
| Low cost of food             |
| Taste of food                |
| Variety of food              |

Environmental factors suggested to reduce physical activity

- Reduced need for physical labor in most jobs
- No required physical activity in schools
- Reductions in physical activity required for daily living, no sport
- Competition from attractive sedentary activities:
  - Television, video/DVD, computer games, internet

ENERGY BALANCE

Energy balance consists of intake regulation and energy expenditure of the body. These two are influenced by:

1. Psychological aspect
2. Organobiological aspect in form of energy homeostasis that consists of:
   a. Energy intake regulation
   b. Energy expenditure regulation

In general, the pathogenesis of obesity can be described in as figure 1.

PSYCHOLOGICAL ASPECT

Perception of hunger is many times determined by mood, place, taste, type of food, eating behavior in family, local culture and eating motivation. Energy expenditure is much influenced by decreased motivation to exercise due to facilities and technology and lack of understanding on the benefit of physical activity for health maintenance.

ORGANOBIOLOGIC/HOMEOSTASIS ASPECT

Physiologically, energy intake is derived from food. The energy is produced to maintained basal metabolic rate (obligatory energy expenditure), adaptive thermogenesis energy and energy for working.

There is physiological balance between energy intake and expenditure which is described in figure 2. Energy allocation is further described in figure 3.
If there were increased intake or decreased energy expenditure, the body would try to reduce excess energy and lower intake or increase energy expenditure. The extra energy in the long term will be stored in form of fat mass in adipose tissue. Protein and carbohydrate storage is relatively stable, thus, condition that determines the bodyweight in the long term is adipose tissue mass.

A. Energy/food intake regulation
Physiologically, food intake is controlled by appetite which is the result of stimulus interaction of food and its inhibitors. Food stimulation is caused by increased need and expenditure of energy in the form of hunger sensation, while the inhibitory factor is in the form of satiety. Hunger is influenced by internal factors such as blood glucose, insulin, ghrelin and external factors like emotion, time, food availability and environment factors. The sense of satiety has more roles in determining food quantity and much more influenced by internal factors. There is feedback mechanism of food intake regulation that consists of:

- Center of intake regulation and energy expenditure
  Hypothalamus is the center of information that receives and processes regarding energy balance status in the body through afferent signal derived from gastrointestinal tract and adipose tissue. Ventromedial hypothalamic nuclei (VHN) stimulation causes the release of neuropeptide of ‘satiety’ sensation. On the other hand, stimulation of lateral, dorsomedial and paraventriculi hypothalamic nuclei cause the release of neuropeptides of ‘hunger’. At the hindbrain, there are solitary tract nuclei (STN) which receive signal from gastrointestinal tract. Third brain ventriculi had arcuata nuclei which function as peripheral signal transducer to special neuronal signal. Those various nuclei are connected to one another and send signals through neurons to cerebral cortex, hypofisis brain stem cell and autonomic nerve system.

- Afferent Signal of Intake Regulation
  There are 2 afferent signals which are classified as hormonal and neuronal signal:

1. Hormonal signal
   This afferent signal comes from adipose tissue, gastrointestinal tract, thyroid glands, adrenal, muscles and reproductive organs where signals from the two first mentioned organs have more roles. These signals deliver information on nutritional balance and body fat mass. Functionally, hormonal signal consists of short term signal coding of satiety, while the longterm signal code energy balance in adipose tissue (adipocyte signal).}

   a. Peripheral afferent signal of gastrointestinal tract
      During eating and digestion process, cholecystokinin (CCK) is released due to mechanical stimulation of gastric stretching. This hormone delivers afferent signal through vagal nerve to STN which then projects it to hypothalamus, insular cortex and motoric nuclei of brain stem cell resulting in sign of cessation of eating processes. Many kinds of afferent signals from gastrointestinal tract are shown in table 2.

   b. Peripheral afferent signal of pancreas
      Insulin, glucagons, and amylin are food intake regulators. Physiological afferent signal of pancreatic hormones are shown in table 3.

   c. Adipocyte signal
      In condition of excess energy exists, secretion of insulin and leptin will increase as adipose signal that gives information to hypothalamus. On the contrary, in condition of insufficient energy, there is increase of ghrelin. Adipose signal is a long term signal although ghrelin and insulin are rather short term signals.

Leptin
Leptin is coded by LEP gene at chromosomes 7q31. This substance is assumed as one of cytokine family due to its crystal structural form. Leptin is mainly produced in the night by white adipose tissue although it is also produced by the brown adipose tissue, gastric mucosa, macrophage, mammary epithelium, myocytes, and placenta as well. Leptin level is in accordance with visceral adipose tissue, circulates freely or protein binds and is able to run across the blood brain barrier. In condition of long fasting, leptin level will decrease and the other way goes in excess food intake. Leptin possesses receptors coded by gene 1p31. There are 5 types of leptin receptor (LEP-Ra, LEP-Rb, LEP-Rc, LEP-Rd and LEP-Re) in hypothalamic tissue, brain, lung, renal, muscle, liver, pancreatic β-cell, adrenal, hemopoietic stem cell, ovary, and adipose tissue. Leptin secretion is increased by high dose insulin, glucocorticoids, and estrogen, while isopreterenol, adrenal β3 receptor agonist, nicotine, high Zn diet, thiazolidinediones, testosterone, and thyroxine will decrease it. Because leptin secretion is in line with the amount of fat mass tissue, thus obese patients have high level of leptin. This fact has explained the role of leptin resistance in pathogenesis of obesity. Physiology of leptin consists of: a).Central physiology; by binding with LEP-Rb in arcuate nuclei, leptin inform the condition of excess energy to hypothalamus through sympathetic
nerve system. This binding will then send signal through JAK-2 (janus kinase-2) and signal transducer and activator of transcription 3 (STAT-3) in thyrosine kinase pathway that will suppress the expression of ‘hunger’ neuropeptide effector (orexigenic). Main orexigenic substance are neuropeptide Y (NPY) and agouti related protein (AGRP). Leptin increases sympathetic activity which modulates thermogenesis through mitochondrial uncoupling protein (UCP) induction of brown adipose tissue.

Peripheral physiology; Leptin modulates peripheral signal of ‘satiety’ such as CCK signal. In addition, it inhibits lipogenesis through inhibition of acetyl-CoA carboxylase that makes malonyl-CoA as mitochondrial b-oxidative inhibitor substance decrease. Leptin increases mitochondrial oxidation and lipolysis and make intracelullar fatty acid and triglyceride decrease. Insulin resistance and lipogenesis in liver will decrease. Insulin receptor in ARC posseses anorexigenic property and contains of a-subunit as insulin binding.

### Table 2. Afferent Signals from Gastrointestinal Tract

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Stimulus</th>
<th>Site of Production</th>
<th>Site of Action</th>
<th>Effect on food intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCK</td>
<td>Protein and fat</td>
<td>Small intestine</td>
<td>Vagal afferents</td>
<td>Decrease</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Nutriens</td>
<td>Ileum/colon</td>
<td>Gastric emptying</td>
<td>Decrease</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Fasting</td>
<td>Stomach</td>
<td>Brain/ARC</td>
<td>Increase</td>
</tr>
<tr>
<td>Apo A-IV</td>
<td>Fat absorption</td>
<td>Intestine/liver</td>
<td>Brain/ARC</td>
<td>Decrease</td>
</tr>
<tr>
<td>Enterostatin</td>
<td>Fat absorption</td>
<td>Stomach/Intestine</td>
<td>Vagal afferents</td>
<td>Decrease</td>
</tr>
<tr>
<td>Bombesin</td>
<td>Gastric mucosa</td>
<td>Food ingestion</td>
<td>Vagal afferents</td>
<td>Decrease</td>
</tr>
<tr>
<td>PYY 3-36</td>
<td>Carbohydrate, fat</td>
<td>Small intestine,</td>
<td>Brain/ARC</td>
<td>Decrease</td>
</tr>
<tr>
<td>Oxyntomodulin</td>
<td>Carbohydrate, fat</td>
<td>Colon</td>
<td>Brain/ARC</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

### Table 3. Regulatory Peptide of Food Intake/Apheren Signal of Pancreas

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Stimulus</th>
<th>Site of Production</th>
<th>Site of Action</th>
<th>Effect on food intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Carbohydrate</td>
<td>β-cell</td>
<td>Brain</td>
<td>Decrease</td>
</tr>
<tr>
<td>Amylin</td>
<td>Carbohydrate</td>
<td>β-cell</td>
<td>Brain</td>
<td>Decrease</td>
</tr>
<tr>
<td>Glucagon</td>
<td>Cephalic response</td>
<td>α-cell</td>
<td>Liver/vagal afferents</td>
<td>Decrease</td>
</tr>
</tbody>
</table>
location and b-subunit with thyrosine kinase as intracellular protein signal activator. Protein produced by b-subunit that is called insulin receptor substrate 1 (IRS-1) is coded by tubby gene (Tub). Disturbance on Tub gene causes obesity. Insulin injection to third brain ventriculi increases anorexigenic effect of CCK and corticotropine releasing factor (CRF) mRNA expression and decreases NPY expression. It is clear that insulin has the catabolic effect on central nervous system. When the level of insulin goes high, insulin influx rate into the brain is not increased. Insulin also has a role in long term signal processing through its ability to determine how much fat is needed and stored in the body. Insulin effect in peripheral and central nervous system seems to counteract each other.14,16,18,20

**Association Between Peripheral Afferent Signal and Adiposity Signal**

Association between peripheral signal afferent and adipose signal in intake regulation is shown in figure 4.

**Interaction Between Adiposity Signals in Hypothalamus**

Hypothalamic ARC neurons are classified into 2 groups. First group expresses propiomelanocortin (PMC) neuropeptide and Cocaine and amphetamine regulated transcript (CART), while the second group expresses NPY and AGRP. Leptin and ghrelin have receptors on both group of neurons but with counteract expression. Leptin stimulates POMC/CART and inhibits NPY/AGRP while ghrelin acts the other way round. Leptin signal disturbance increases sensitivity to ghrelin but the other counterparts issues had not yet been proven.14,20,27

NPY/AGRP neurons send local collateral input through gamma amino butyric acid (GABA) to POMC/CART neurons. This will suppress POMC/CART and stimulate the appetite. Ghrelin precipitates this local circuit while ghrelin inhibits it.14,27 Association between adipose signals in hypothalamus in intake regulation can be seen in figure 5.

The similarity between leptin and insulin receptor location is POMC neurons. Both work synergistically resulting in hypophagia effect. An intracellular insulin mediator called phosphatidyl 3-OH kinase is also known to increase transduction of leptin anorexigenic signal. The difference between these two signals is that insulin signal describes more short term metabolic changes while leptin has more roles in the long term changes. Insulin secretion is in line with visceral white fat mass, while leptin secretion represents total amount of body fat.13,18,19,23

2. Neuronal Signal System

The system is controlled by sympathetic and serotonergic nervous system which possesses axis that is very similar to adiposity signal axis. The role of sympathetic nerve system in regulating of energy intake is done by 2 actions. First by increasing thermogenesis through norepinephrine release which causes stimulation of mitochondrial UCP system. The second one is through increasing epinephrine release that will induce glucose and fatty acid oxidation. Serotonin neurons in dorsal raphe nucleus midbrain sends signals to PVN and VMH neurons through POMC neuron system resulting in decreased food intake. Damage of serotonin receptor 2C (5-HT2CR)
causes hyperphagia and obesity. Sympathetic neuronal signal system is also influenced by corticosteroids, estrogen, testosterone, and thyroxine.\textsuperscript{14,17}

- Effectors system of intake regulation
  As the response to various afferent signals, hypothalamus send efferent signals to arcuate nuclei which then produce some effector neuropeptides of feedback mechanism regulatory pathway of food intake. Those neuropeptides are classified into 2 groups; orexigenic and anorexigenic neuropeptides.\textsuperscript{15-16} Biological effectors of food intake are shown in table 4.

B. Energy expenditure regulation
Nutrients derived from food digestions will undergo oxidative phosphorylation in mitochondria to form adenosine-triphosphate (ATP) by releasing energy in form of heat. The use of ATP and physical activity also releases heat. This process is initiated by sympathetic stimulation on \(\beta_3\)-adrenergic receptor. The receptor stimulation will activate protein kinase A effectors and cyclic adenosine monophosphate (c-AMP) that has 2 effects. The first is an acute effect of increased lipolysis and activation of UCP-1 on brown fat tissue and UCP-2 and UCP-3 of muscles. The second is a chronic effect such as UCP gene transcription, mitochondrial biogenesis, hyperplasia, and brown adipose tissue recruitment to white adipose tissue. POMC system regulates energy expenditure through \(\alpha\)-MSH neurons on melanocortin receptor 4 (MC-4) by activating sympathetic nervous system. Activation of POMC neurons is initiated by leptin when energy storage in fat tissue is increased.\textsuperscript{13,15,16} Regulation of energy expenditure is shown in figure 6.

\section*{TREATMENT OF OBESITY}
Treatment of obesity includes pharmacologic and nonpharmacologic therapy. Non pharmacologic therapy consists of dietary program, life style and eating habit modification, exercise and surgical therapy. Weight loss is gained gradually. Longterm goal of therapy is 10 \% of weight loss from the initial body weight, maintain BMI < 23 kg/m\(^2\), lowering blood pressure and blood glucose, risk factor management of obesity and glycemic control.\textsuperscript{7,11,28-30} Surgical therapy is indicated in:
1. Patient with obesity with BMI > 40 kg/m\(^2\) and or body weight \(\geq 45\) kg above mean normal weight of population after age and sex adjustment
2. Patient with obesity with BMI 35-40 kg/m\(^2\) and has comorbid like type 2 diabetes mellitus, hypertension, heart failure, peripheral edema, sleep-apnea syndrome, bronchial asthma, severe dyslipidemia, esophagitis, cerebral pseudotumor, osteoarthritis, thromboembolic disorder and urinary incontinents.\textsuperscript{7,11,29}

\section*{PHARMACOLOGIC THERAPY OF OBESITY}
In general, the classification of obesity drugs are as follows:
1. Drugs that suppress the appetite (appetite suppressants)
2. Drugs that inhibit nutrients absorption
3. Drugs that increase energy expenditure but have not been approved for treatment of obesity such as ephedrine.\textsuperscript{27,29}

Obesity drugs that will be discussed below are those have been approved by the FDA, are shown in table 5.
Norepinephrine can suppress appetite if binding to adrenoreceptor α1, β2, and β3. This class of drug is receptor agonist and norepinephrine reuptake inhibitor. For examples, diethylpropion, benzphetamine and phentermine. These drugs can increase neuronal norepinephrine release and cause weight loss 3%-8% more than placebo. The side effect is sympathetic tonus overdrive. Because of the potent side effect, FDA did not recommend the use of appetite suppressants for more than 12 weeks.

Sibutramine
This drug inhibits norepinephrine presynaptic reuptake and serotonin so that the effects of both neurotransmitters in central nervous system will increase. In a multicenter study in Europe, sibutramine at doses of 10-20 mg/day along with low calories diet had lost weight 5%-10% in 6 months. Body weight maintained successfully for 2 years in 80% subjects. It could decrease triglyceride level as much as 4.5-42 mg/dl and increase HDL cholesterol as much as 3-9 mg/dl. The side effect of the drug is increased systolic pressure 0.3-2.7 mmHg and diastolic pressure 1.6-3.4 mmHg and increased heart rate 2-5 beats/minute. Intermittent therapy of sibutramine for 12 weeks along with placebo for 7 weeks during period of 48 weeks may reduce the side effect.

Orlistat
This drug inhibits pancreatic lipase enzyme so that hydrolysis of triglyceride to fatty acids lowers and reduces fat absorption as low as 30%. There is no severe systemic effect reported although fat soluble vitamin supplementation is needed. Side effects like diarrhea and flatulence are relatively tolerated. Low calorie diet and orlistat for 6 months resulted in weight loss of 5.9%-10%. Orlistat reduces total cholesterol level, LDL and systolic and diastolic pressure significantly. To reduce the side effect of orlistat, it is recommended to use psyllium mucilloid concomitantly. There is no synergistic effect on combination of orlistat and sibutramine.
PHARMACOLOGIC THERAPY IN THE FUTURE

The drugs in the market recently have only shown potency to reduce weight not more than 10%. Thus, it encourages the search for new promising obesity drugs.

Leptin

This substance stimulates POMC neurons and inhibits NPY neurons resulting in decreased sensation of hunger. A study that used leptin recombinant until reach dose of 0.3 mg/kg had failed to make significant weight loss. This is assumed to be caused by leptin resistance. Low dose leptin as matter of fact inhibits plasma thyroid hormone and prevents energy expenditure reduction as compensation of diet therapy. Thus, leptin is used more to prevent weight gain after other anti obesity therapy than to reduce weight itself. Strategy to cope with leptin resistance is to activate leptin signal cascade from its receptor, ciliary neutrophic factor, a cytokine STST-3 signal activator that can reduce leptin resistance is also being studied.27,29

MC4 Agonis Receptor

A study found that this intranasal drug may reduce 1.68 kg fat mass, decrease leptin and insulin plasma each as much as 24% and 20% subsequently after use for 6 weeks.27

Other Drugs

Ghrelin inhibitor, MCH receptor inhibitor, 11-b hydroxysteroid dehydrogenase antagonist, enzyme that converts cortisone to cortisol in adipose tissue and liver and reduces effect of leptin in hypothalamus is still in ongoing study.27,29

CONCLUSION

Three main factors regarding pathogenesis of obesity are genetics, environment and energy balance. Obesity may be caused by increased intake or decreased body expenditure. Energy intake is mainly regulated by appetite especially the sense of satiety. Feedback mechanism of appetite regulation consists of center regulation in hypothalamus, various afferent signals and neuropeptide effectors. Short afferent signal comes from the gastrointestinal tract while the longterm signal comes from the adipose tissue. Interaction between leptin with insulin and ghrelin on POMC and NPY neurons in hypothalamus regulates the intake. Obesity may be caused by leptin resistance, hyperinsulinemia, ghrelin hypersecretion or disturbed interaction between the three substances. Other energy regulation systems are serotonine and cathecolamine systems. Energy expenditure is mainly regulated by sympathetic systems through adrenergic receptor β3 by mitochondrial activation. Pharmacologic therapy of obesity commonly known recently still cannot decrease bodyweight significantly and this has encouraged the searching of newly promising obesity drugs.
REFERENCES